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（海外特別研究員事業）

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海外特別研究員最終報告書

独立行政法人 日本学術振興会 理事長　殿

採用年度　平成２９年
受付番号　１２１
氏　　名　小島　正寛
（氏名は必ず自署すること）

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：バークレー　（国名：米国　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
新規中枢神経疾患医薬リード創出を指向したlate-stageアダマンチル化反応の開発

3. 派遣期間：平成　２９年　７月　１日　～　平成　３０年　３月　１９日

4. 受入機関名及び部局名
カリフォルニア大学バークレー校化学科

5. 所期の目的の遂行状況及び成果…書式任意　**書式任意（A4 判相当 3 ページ以上、英語で記入も可）**
（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）
（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

Development of late-stage adamantylation reactions for the discovery of new CNS drug leads

Masahiro Kojima
Department of Chemistry, University of California, Berkeley, The Hartwig Group

[Introduction]

Drug discovery for central nervous system (CNS) is a big challenge in this aging society. Difficulty in CNS drug development stems from blood brain barrier (BBB), a physiological gatekeeper that blocks hydrophilic biomolecules from entering the brain. Although monoclonal antibodies or peptides are increasingly utilized in cutting edge cancer treatment, these classes of molecules cannot reach our brain because of BBB. I envisioned that late-stage adamantylation of pharmaceuticals would enable them to penetrate BBB because of the uniquely high lipophilicity of adamantane derivatives (Figure 1). The adamantylation reaction is going to be realized by the merger of radical chemistry and copper catalyzed cross coupling (Figure 2).

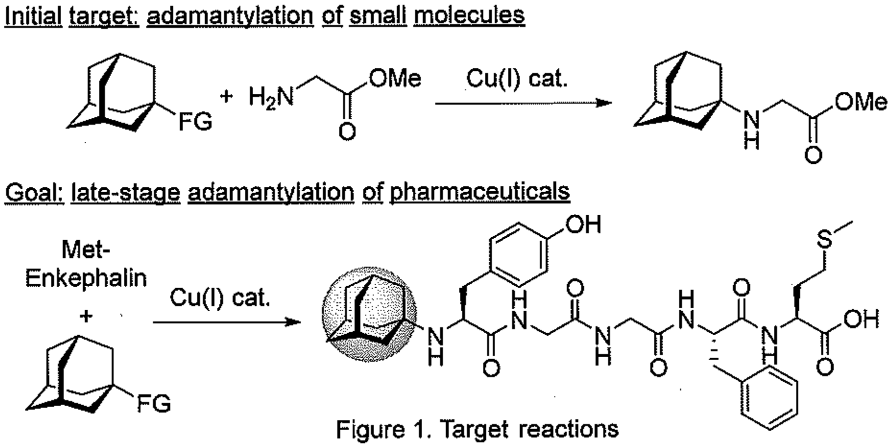

Figure 1. Target reactions

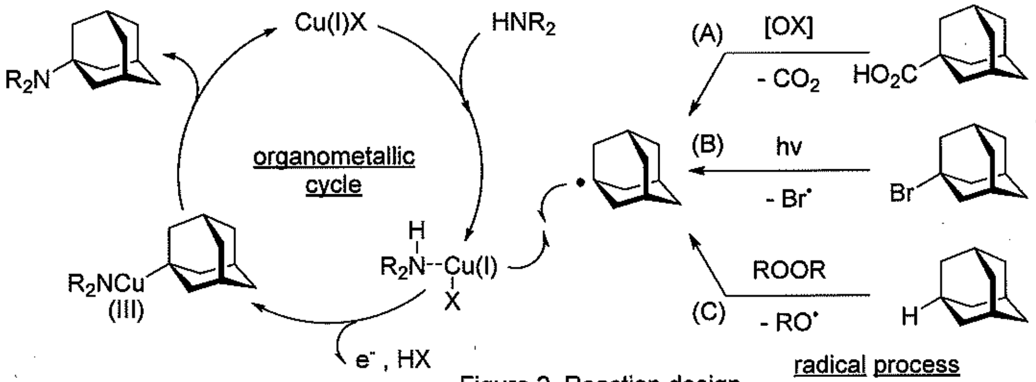

Figure 2. Reaction design

[Research direction]

As one extension of the proposed adamantylation reaction of nitrogen, we envisioned that establishment of general synthetic methodology to access carboxylic acids via C-H bond functionalization of complex molecules would realize the derivatization of amines with pharmaceutically important structures as well as adamantane. Functionalization of inert C-H bonds have been recognized as a conceptually new strategy for the transformation of organic compounds (*J. Am. Chem. Soc.* 2016, *138*, 2). Among all, selective functionalization of sp3 C-H bonds is desirable, since sp3 C-H bonds are one of the most common structural motif in natural products, pharmaceutical agents, agrochemicals and so on. However, due to intrinsic low reactivity and abundance of sp3 C-H bonds, their selective functionalization remains a formidable challenge in synthetic chemistry.

In 2012, Hartwig group disclosed an alcohol-directed, iridium-catalyzed selective silylation of inert sp3 C-H bonds (*Nature* 2012, *483*, 70). This transformation distinguishes itself from an array of directed sp3 C-H bond functionalization, as it provides medicinally relevant 1,3-diol scaffolds from simple alcohols (Figure 3).

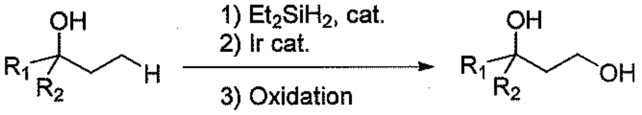

Figure 3. Alcohol-directed sp3 C-H bond functionalization

Late-stage functionalization of complex molecules is a promising approach for the preparation of drug leads with improved biological activity. While C-H bond functionalization is suitable for this purpose, reactions with high level of selectivity and functional group tolerance are yet limited. I hypothesized that the alcohol-directed C-H functionalization might be applicable to late-stage derivatization of complex molecules and thus afford complex carboxylic acids for the copper-catalyzed functionalization of amines. Indeed, previous results suggest that the alcohol-directed sp3 C-H bond functionalization is applicable to some naturally occurring terpenes (Figure 4). I was working on the evaluation of generality and limitations of the iridium-catalyed reactions in the context of natural product derivatization.

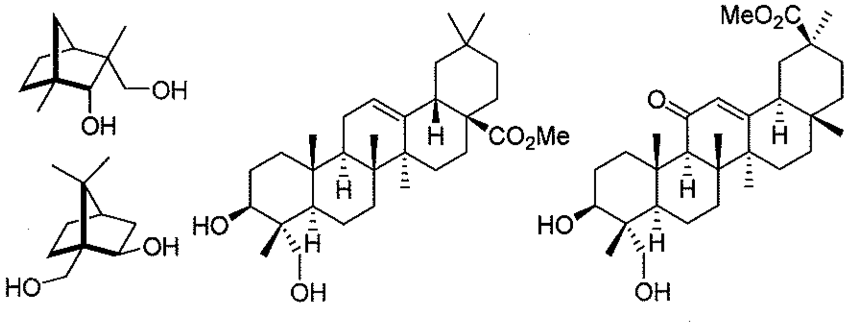

Figure 4. Selective functionalization of sp3 C-H bonds of terpenes

[Results]

Under the standard conditions, selective functionalization of sp3 C-H bonds were feasible in a series of natural product derivatives (Figure 5). These results support that the current method is suitable for the late-stage derivatization of complex molecules. On the other hand, limited reactivity was observed with some natural product derivatives (Figure 6). Rationalization of the low reactivity and development of new C-H functionalization method for these substrates are ongoing.

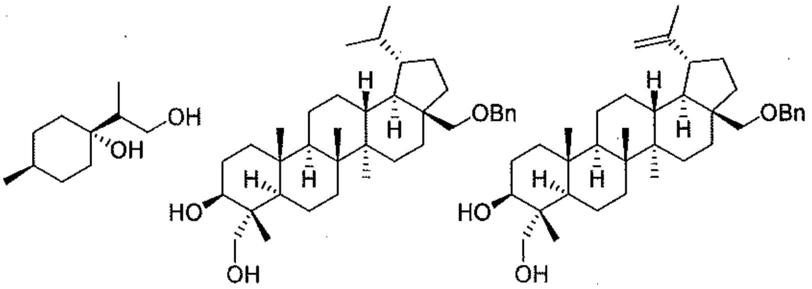

Figure 5. Results for the selective functionalization of sp3 C-H bonds

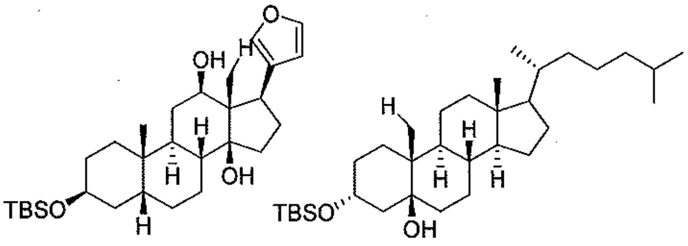

Figure 6. Substrates with limited reactivity

[Future prospects]

1) New linker design for challenging sp3 C-H bond functionalization

In case of substrates with limited reactivity, it is envisioned that conformational aspects account for the low reactivity. In order to overcome these limitations, design of different linker for the C-H functionalization could be one solution. For example, methylsilyl group can be readily installed on and removed from alcohols. Its longer linker length would provide new environment for the directed C-H silylation (Figure 7).

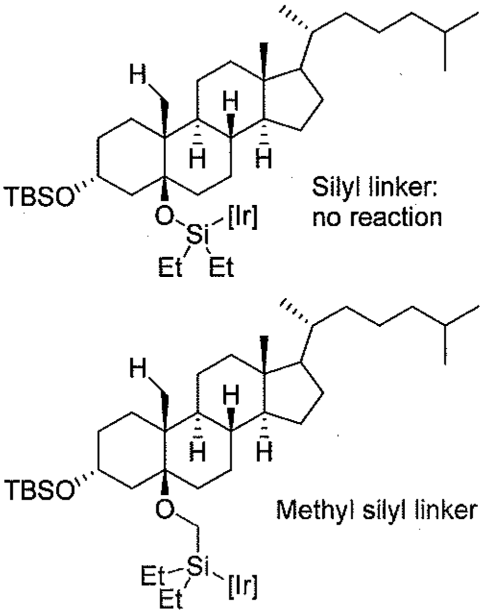

Figure 7. Design of new linker

2) Functionalization of amines with natural product-derived carboxylic acids

The newly installed hydroxy group should be considered as a precursor for carboxylic acids. With the complex carboxylic acids, it is reasonable to assume that the reaction design for decarboxylative adamantylation of amines is applicable for the natural product-derived carboxylic acids. Thus, the copper-catalyzed protocol is under investigation in the group.